AD 268 437

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Report to Commanding Officer
Chemical Warfare Laboratories
Army Chemical Center
ATTN: Mr. B. Kagan, Project Officer

Contractor: University of Oregon
Contract No: DA-CML-18-108-61-G-5

Final Report

Covering the Period
September 15, 1960 through September 14, 1961

Title: Investigation of Calabash Curare

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The objective of the present study was the elucidation of structure of the important alkaloids of calabash curare. In addition samples of interesting materials were to be submitted for testing and sofar as feasible a correlation between structure and physiological activity would be attempted.

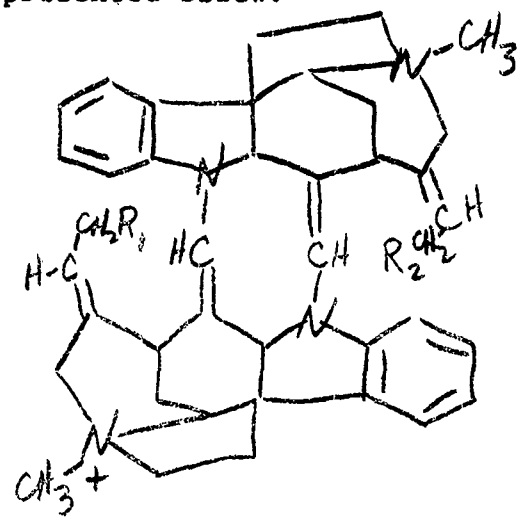
At the beginning of this work, there were three other laboratories active in the investigation of calabash curare. These included the group at Zurich headed by Karrer and Schmid, at Frankfort headed by Theodore Wieland, and at Bristol headed by Battersby. During this past year development in our knowledge of calabash curare has continued at a rapid pace and all four laboratories have contributed to this. Since this is a report of work done under our contract, the discussion will emphasize our own contributions. However, it should be made clear that we appreciate the importance of the contributions from the other laboratories and realize that each has been aided by the work of the others.

At the start of our work under this contract, it was recognized that the most important alkaloids of calabash curare could be arranged in three families and these are listed below.

C-Dihydrotoxiferine	C-Curarine-I	C-Calebassine
C-Alkaloid-H	C-Alkaloid-G	C-Alkaloid-F
C-Toxiferine-I	C-Alkaloid-E	C-Alkaloid-A

The structures of the first two, the dihydrotoxiferine and C-curarine-I families, have now been established, although the structures of the calebassine family remain uncertain. These

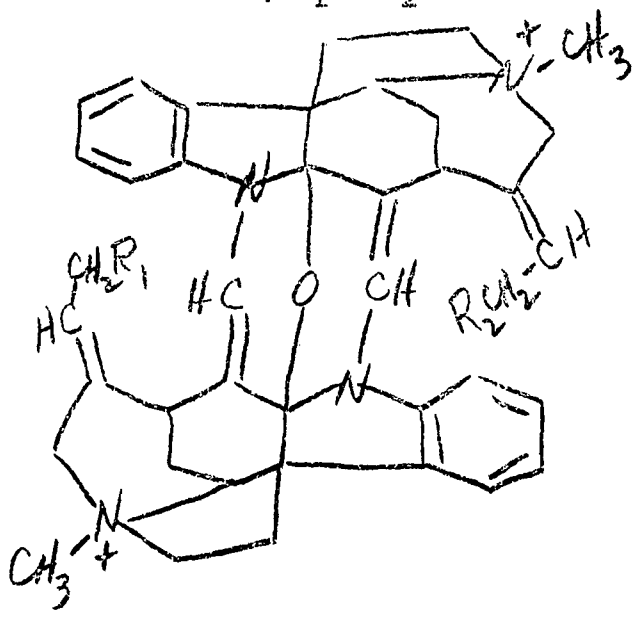
structures are presented below.



C-Dihydrotoxiferine, $R_1 = R_2 = -H$

C-Alkaloid-H, $R_1 = -H$; $R_2 = -OH$

C-Toxiferine, $R_1 = R_2 = -OH$



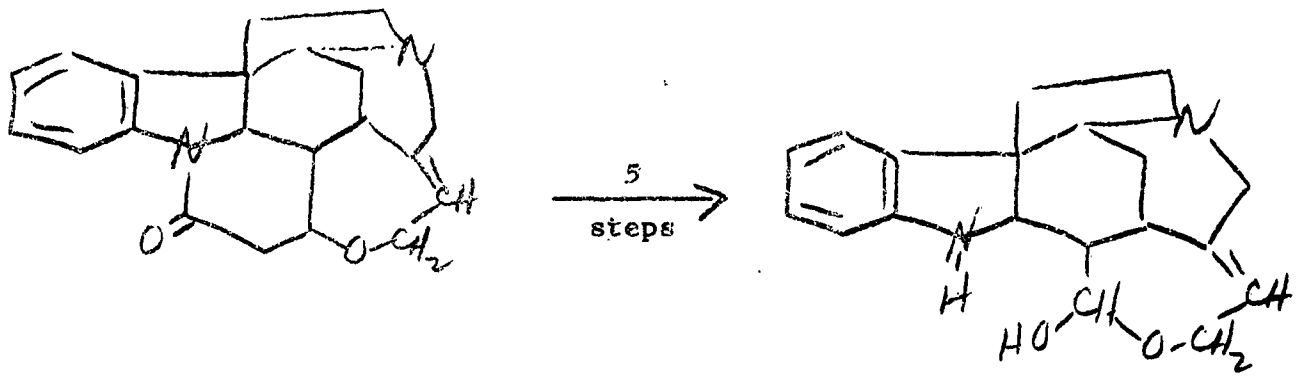
C-Curarine-I, $R_1 = R_2 = -H$

C-Alkaloid-G, $R_1 = -H$, $R_2 = -OH$

C-Alkaloid E, $R_1 = R_2 = -OH$

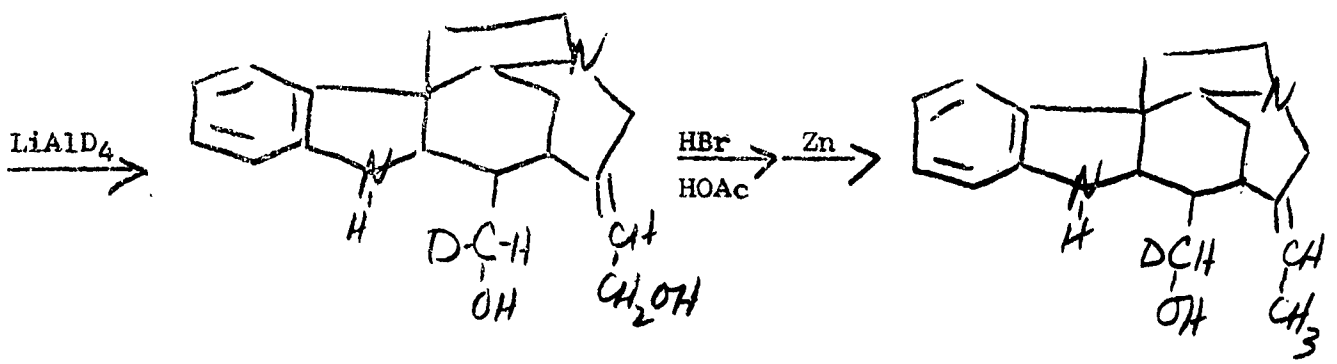
These deductions have stemmed primarily from NMR studies, both on the alkaloids themselves and their deuterium substituted derivatives. The introduction of deuterium proved to be a rather difficult task but it has now been successfully accomplished and the reactions employed for the syntheses of the deuterodihydrotoxiferine and deuterotoxiferine are outlined below.

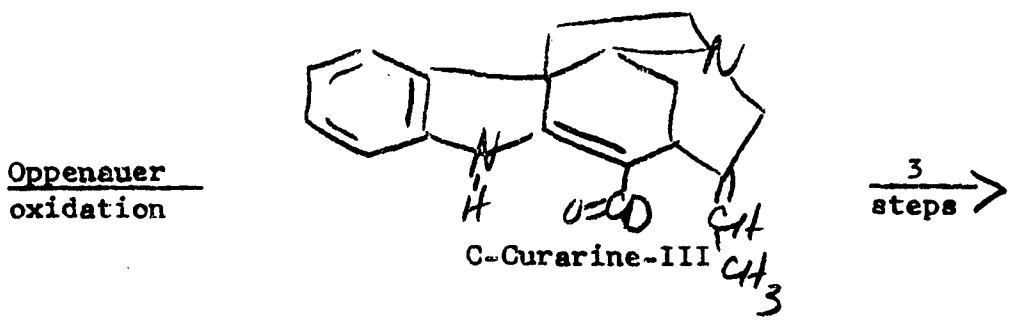
Synthesis of Deuterodihydrotoxiferine



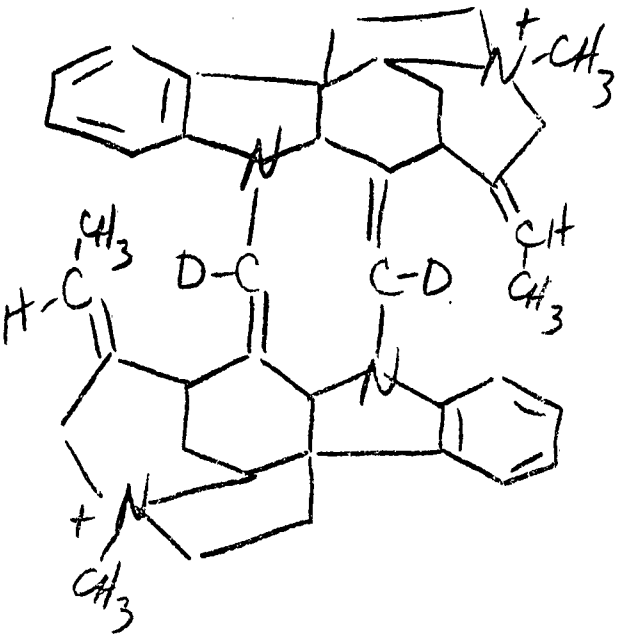
Strychnine

Wieland-Gumlich Aldehyde



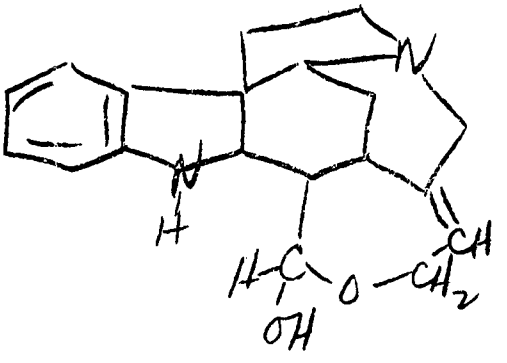


C-Curarine-III



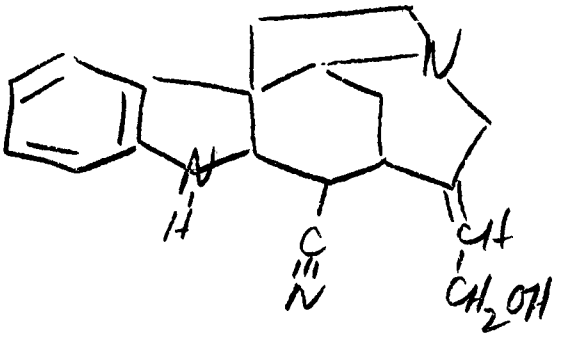
Deuterodihydrotoxiferine

Synthesis of Toxiferine



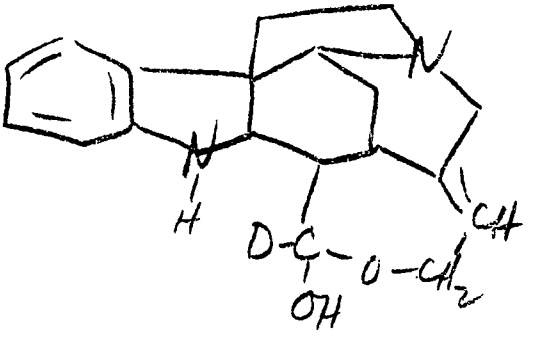
Oxime

Wieland-Gumlich
Aldehyde



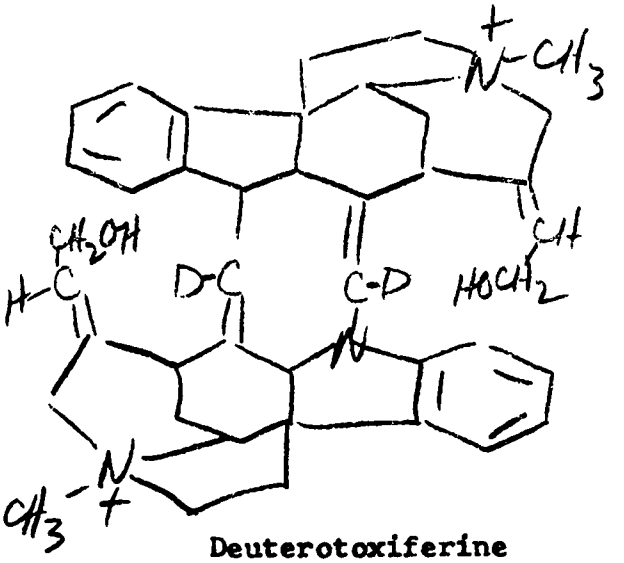
→ methyl ester → dimethyl amide

$LiAl(OEt)_2D_2$ →



→ 3 steps →

Deutero-Wieland-Gumlich Aldehyde



Deuterotoxiferine

By comparison of the N.M.R. spectra of the protonated and deuterated species it has been possible to decide which signals are to be associated with positions in question. In turn, from this the chemical shift and spin-spin splitting allows deductions regarding the structure of the immediate environment.

Investigations of the structure of calebassine and its associated alkaloids as well as that of lumi-dihydrotoxiferine are still under investigation.

The structural investigations of polyneurine have been curtailed due to the limited availibility of the compound. We are at present investigating the application of mass spectrometry to the tertiary amine derived from the alkaloid by lithium aluminum hydride reduction.

Dr. Trevor Crabb and Dr. David Nelson have been associated with this project during the past year.

Publication of much of the work described above is still in process. One publication on the structure of dihydrotoxiferine has appeared.[1]

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[1] V. Boekelheide, O. Ceder, T. Crabb, Y. Kawazoe, and R. N. Knowles, Tetrahedron Letters, 26 1 (1960).